Research Week 2023

Inflammatory signaling in the liver drives early metabolic disruption in pancreatic cancer cachexia

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Keywords

Pancreatic cancer, cachexia, STAT3, IL6, ketogenic diet

Abstract

Cancer cachexia is a co-morbidity highly prevalent in pancreatic ductal adenocarcinoma (PDAC) patients and results in a decreased quality of life. Cachexia is characterized by losses in muscle and adipose tissue mass, which are persistent and refractory to interventions such as nutritional support. We documented that early-stage cachexia is characterized by increased sensitivity to nutritional stress. In healthy animals under nutritional stress, the liver shifts metabolism to supply energy-rich molecules (ketone bodies, glucose) to fuel the brain, heart, and skeletal muscle. We hypothesized that hepatic adaptive metabolism is impaired in PDAC cachexia, creating a state of nutritional fragility and resulting in accelerated skeletal muscle wasting. Recent literature highlights the relationship between interleukin 6 (IL-6) signaling and PDAC cachexia. We hypothesized that in addition to acting directly on muscle and adipose tissue, IL-6 acts on the liver to drive metabolic changes associated with impaired adaptive response to undernutrition. We tested these hypotheses using a murine model of PDAC, where adult mice received orthotopic injections of the PDAC cell line *$Kras^{G12D}$; $p53^{R172H/+;}$ Pdx1-cre (KPC)*. PDAC mice displayed suppressed fasting blood ketone levels and octanoate challenge revealed impaired ketogenic potential in PDAC mice. This associated with decreased expression of genes regulating beta oxidation and ketogenesis in the liver (*Ppara, Acox1, Acadm, Hmgcs2, Ehhadh, Acaa2, Bdh1*). Maintaining PDAC mice on a ketogenic diet reversed metabolic deficits and prevented skeletal muscle loss. Genetic ablation of IL-6 (whole body) or STAT3 (hepatocyte-specific) recapitulated this effect and led us to conclude that IL-6 signaling via STAT3 in hepatocytes impairs adaptive metabolism, makes PDAC mice vulnerable to nutritional stress, and promotes muscle wasting. This work expands on prior knowledge of IL-6 in cancer cachexia, implicates impaired hepatic metabolism as an early event in cachexia progression, and highlights the liver as a target for potential interventions in cachexia treatment.